

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Johansen <i>et al.</i>	Confirmation No.:	2372
SERIAL NUMBER:	10/806,793	EXAMINER :	Chang Yu Wang
FILING DATE:	March 22, 2004	ART UNIT :	1649
FOR:	NOVEL NEUROTROPHIC FACTORS		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

I, Teit Johansen, hereby declare and state as follows:

1. I am a named inventor in the above-identified patent application. I am the President and CEO of the assignee of this application, NsGene, a Danish biotechnology company. I have been working in the field of molecular biology since 1984. I hold a PhD in Molecular Biology from the University of Copenhagen. Between 1986 and 1991 I conducted research in molecular biology at the Danish University Hospital, Rigshospitalet. From 1991 through 1994 I worked at Johns Hopkins University in Baltimore, Maryland (in various positions up to Assistant Professor) in the field on molecular biology. From 1994 through 1999 I worked at Neurosearch A/S, in Copenhagen, Denmark, to establish the molecular biology capability of that company. In 1999, I founded NsGene.
2. I am an inventor of the present invention and am familiar with the contents of this application. I have reviewed the Office Action of December 9, 2008 relating to this application and the references cited therein.
4. I understand that the Examiner has maintained an obviousness rejection over the teachings of Yan (U.S. Patent No. 5,641,749) and Milbrandt (U.S. Patent No. 6,284,540). Yan is cited by the Examiner for its teaching that injury of retinal ganglion cells may be treated by administering glial cell line-derived neurotrophic factor (GDNF). Milbrandt is cited by the

Examiner for its teaching of neublastin/artemin (NBN/ARTN) and for the classification of NBN/ARTN into the GDNF family of growth factors. In maintaining this rejection, the Examiner alleges that Milbrandt teaches that “NBN/ARTN can bind and activate GFR α 1” and that “not only does NBN/ARTN belong to the GDNF family, it also functions as GDNF.”^{1/} These conclusions, however, are not factually supported by Milbrandt, nor are they supported by the general understanding in the art, which is further explained below.

5. First, Milbrandt does not teach that NBN/ARTN can bind and activate GFR α 1. Nor does Milbrandt teach the *in vivo* activation of GFR α 1 by NBN/ARTN. Rather, in Example 7, Milbrandt expressly states that the GFR α 1-Fc fusion protein did not bind NBN/ARTN.^{2/} And, again in Example 8, Milbrandt reiterates that “direct binding of artemin to GFR α 1-Fc ... was not observed.”^{3/}
6. The present Specification also provides data to show that ARTN/NBN exhibits high affinity for GFR α -3, and that GDNF does not bind to GFR α -3, but rather binds to GFR α -1.^{4/} Specifically, the Specification highlights the functional difference between ARTN/NBN and GDNF as follows:^{5/}

[N]eublastin binds to GFR α -3 but not to GFR α -1. This behavior clearly distinguishes neublastin from GDNF; as shown in FIG. 11, GDNF binds to GFR α -1 but not to GFR α -3.

It is clear from this data that GDNF acts on GFR α -1 and ARTN/NBN acts on GFR α -3 and that there is no cross-talk.

7. Milbrandt, in Example 7, discusses the results of *in vitro* receptor activation experiments, in which GFR α -1 was over-expressed in neuroblastoma cells, where activation of GFR α -1 was seen with the high level of expression of GFR α -1 in response to ARTN/NBN. These results, however, are not physiologically significant, but rather an artifact of the experimental

^{1/} Office Action at page 3, lines 18-22.

^{2/} Milbrandt at column 39, line 66 to column 40, line 1.

^{3/} Milbrandt at column 42, lines 6-11.

^{4/} See e.g., Specification at Figure 11.

^{5/} Specification at page 55, lines 19-21.

conditions. Indeed, Rakowicz^{6/}, specifically teaches that GDNF is the exclusive physiological ligand for GFR α -1. It is important to note that Milbrandt himself is co-author of this report and that ARTN/NBN was also tested and compared to GDNF. Specifically, Rakowicz at page 3958, left column, last paragraph provides as follows:

“To examine the physiological importance of GFR α -1 for GDNF-dependent motor neuron (MN) survival, slice cultures were prepared from *GFR α -1*^{-/-} mice and cultured in the presence of GDNF or no trophic factor. The survival response to GDNF was completely abolished in *GFR α -1*^{-/-} neurons (Fig. 7C). Thus, the trophic effect of GDNF on MNs is completely mediated by the *GFR α -1* co-receptor. Furthermore, despite *in vitro* evidence in cell lines of potential cross talk between different GFL members and their respective receptors [...], in this paradigm only GDNF induces a significant MN survival signal through *GFR α -1*. The absence of a detrimental effect of the other GFLs when coadministered with GDNF suggests that they do not compete with GDNF for receptor binding.”

In addition, on page 3960 of Rakowicz, Figure 7 (as mentioned in the above cited text) provides an overview of these results clearly showing that GDNF is the exclusive physiological ligand for GFR α -1 and that none of the other GDNF-family ligands can promote survival of the motor neurons; and that none of them compete with GDNF for binding to GFR α -1. On the same page, right column the paragraph headline states that “*GDNF is the exclusive physiological ligand for GFR α -1*”, and the last sentence in that paragraph states: “Thus not only were none of these factors in isolation survival-promoting for MNs, but they also showed no evidence of competition with GDNF for receptor binding, supporting a model of a physiologically exclusive interaction between GDNF and GFR α -1”.

8. A subsequent study by Carmillo^{7/} confirms the findings of Rakowicz. For example, Figures 1-3 of Carmillo shows that GFR α -1 is highly selective for GDNF as compared to ARTN/NBN. Based on these results, Carmillo concludes that “GFR α -1 is not likely to be a functional coreceptor for ARTN/NBN *in vivo*.”^{8/}
9. In view of the above, it is not a fact that “NBN/ARTN can bind and activate GFR α 1” and that NBN/ARTN can function as GDNF as maintained by the Examiner. ARTN/NBN is

^{6/} *J Neurosci.* 2002 May 15;22(10):3953-62.

^{7/} *Biochemistry.* 2005 Feb 22;44(7):2545-54.

^{8/} *Id.* at Abstract.

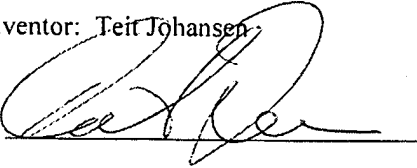
structurally and functionally distinct from GDNF. Indeed, ARTN/NBN does not bind and activate GFR α -1 in a physiologically significant manner.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statement were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.

SIGNATURE:

Full name of joint inventor: Teit Johansen

Inventor's signature:



Date:

March 6, 2008